1: Trends Mol Med 2001 Aug;7(8):355-62 Related Articles, Links



# The calpain family and human disease.

**Huang Y, Wang KK.**

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The number of mammalian calpain protease family members has grown to 14 or last count. Overactivation of calpain 1 and calpain 2 (and their small subunit) has long been tied to acute neurological disorders (e.g. stroke and traumatic brain injury) and recently to Alzheimer's disease. Loss-of-function mutations of the calpain 3 gene have now been identified as the cause of limb-girdle muscular dystrophy 2A. Calpain 10 was recently identified as a susceptibility gene for type 2 diabetes, whereas calpain 9 appears to be a gastric cancer suppressor. This review describes our current understanding of the calpain family members and their mechanistic linkages to the aforementioned diseases as well as other emerging pathological conditions.

Publication Types:
- Review
- Review, Tutorial

PMID: 11516996 [PubMed - indexed for MEDLINE]

1: Genomics 1997 Oct 1;45(1):175-84 Related Articles, Links



# A new subfamily of vertebrate calpains lacking a calmodulin-like domain: implications for calpain regulation and evolution.

**Dear N, Matena K, Vingron M, Boehm T.**

German Cancer Research Center, Heidelberg, Germany.

Calpains are calcium-dependent intracellular nonlysosomal proteases that are believed to participate in signal transduction. In vertebrates, five different calpains have so far been identified, of which three, mu-, m-, and mu/m-calpain are ubiquitously expressed while the other two, nCL-1 (p94) and nCL-2, exhibit a restricted tissue distribution. We have identified two new vertebrate calpain genes, Capn5 and Capn6. The human and mouse amino acid sequences of these new calpains are the most divergent of the vertebrate calpains identified. They possess most of the residues conserved in calpain family members but the C-terminal region lacks any homology to the calmodulin-like domain of other vertebrate calpains. They both exhibit significant homology over the entire coding region to the protein encoded by the gene tra-3, involved in nematode sex determination, and Capn5 may represent its vertebrate orthologue. The predicted Capn6 protein lacks critical active site residues and may not be proteolytically active. Both genes are differentially expressed in human tissues with highest RNA levels for Capn5 occurring in the testis, liver, trachea, colon, and kidney, while Capn6 is highly expressed only in the placenta sample of the 50 tissues examined. Phylogenetic analysis suggests that the vertebrate calpains arose through a series of gene duplication events that began before the initial divergence of the vertebrate and invertebrate lineages. The discovery of these two new calpains highlights a hitherto unknown complexity of the calpain family with subclasses perhaps possessing different modes of regulation.

PMID: 9339374 [PubMed - indexed for MEDLINE]

1: J Mol Evol 2001 Sep;53(3):191-203 Related Articles, Links

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# Both the conserved and the unique gene structure of stomach-specific calpains reveal processes of calpain gene evolution.

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**Hata S, Nishi K, Kawamoto T, Lee HJ, Kawahara H, Maeda T, Shintani Y, Sorimachi H, Suzuki K.**

Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Japan.

Related Resources

The proteins nCL-2 and nCL-2' are members of the Ca2+-dependent cysteine protease (calpain) superfamily, with stomach-specific expression. Like other typical calpains, nCL-2 has three distinct domains, a protease, a C2-like, and a 5EF-hand Ca2+-binding domain, as well as the N-terminal propeptide region. On the other hand, nCL-2' lacks the C2-like and 5EF-hand domains but is otherwise identical to nCL-2, except for the three C-terminal residues. To examine the stomach-specific and presumed alternative expression mechanisms of nCL-2 and nCL-2', we have cloned and characterized the mouse gene for nCL-2 and nCL-2'. The mouse nCL-2 gene contains at least 23 exons, spanning more than 50 kb, and possesses an exon specific for nCL-2' in the middle. Therefore, nCL-2 and nCL-2' are generated by alternative splicing of the same gene, Capn8. Capn8 shows the highly conserved gene organization of the other typical calpain large subunit genes, CAPN1, CAPN2, CAPN3, CAPN9, CAPN11, and Capn12, except for the unique exon between exon 9 and exon 10 of Capn8, which encodes the 3' half of the nCL-2' transcript. No such exon in th corresponding regions was found in CAPN1, CAPN2, CAPN3, CAPN9, or CAPN11. Gene and cDNA structures of a presumed human orthologue of mous nCL-2, CAPN8, were determined, revealing that it overlaps human CAPN2, the gene for the m-calpain large subunit, in head-to-head orientation at 1q32-41. These features of Capn8 and CAPN8 illustrate a process of calpain gene evolution, i.e., the protease, C2-like, and 5EF-hand domains presumably functioned as independent genes, and the calpain superfamily has evolved by ordered fusions of these ancestral gene units, with subsequent amplifications.

PMID: 11523006 [PubMed - indexed for MEDLINE]

1: Genomics 1998 Feb 15;48(1):117-20 Related Articles, Links



# Genomic organization of mouse Capn5 and Capn6 genes confirms that they are a distinct calpain subfamily.

**Matena K, Boehm T, Dear N.**

German Cancer Research Center, Heidelberg, Germany.

CAPN5 and CAPN6 are recently identified human and mouse genes lacking a calmodulin-like domain with homology to the calpain family of proteases. To clarify their relationship to the known calpains, we have compared their genomi organization and chromosome location with other human calpain gene family members. In the mouse, both genes have 11 introns of identical location, with 6 of these being similar in location to those of the known vertebrate members. Surprisingly, there were no splice junctions in common with the nematode gene tra-3, the calpain with highest homology to CAPN5 and CAPN6. CAPN5 is localized on human chromosome 11, closely linked to the mu-calpain gene CAPN1. CAPN6, which is expressed only in the placenta, is localized on the X chromosome, to which no other calpain has yet been mapped.

PMID: 9503024 [PubMed - indexed for MEDLINE]

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1: J Mol Evol 2001 Sep;53(3):191-203 Related Articles, Links

JOURNAL OF MOLECULAR EVOLUTION

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Department of Applied Biological Chemistry, Graduate School of Agricultural and Life Sciences, The University of Tokyo, Japan.

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PMID: 11523006 [PubMed - indexed for MEDLINE]

1: Gene 2001 Aug 22;274(1-2):245-52 Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

# Identification and characterization of two novel calpain large subunit genes.

**Dear TN, Boehm T.**

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Calpains are a family of related proteins, some of which have been shown to function as calcium-dependent cysteine proteases. CAPN1 and CAPN2, the mos well characterized calpains, consist of a large (80 kDa) and a small (30 kDa) subunit. In mammals, 11 different paralogous genes encoding calpain large subunits have been identified. We report the identification of two further genes, CAPN13 and CAPN14, potentially encoding calpain large subunits. Radiation hybrid mapping localized both genes within a region mapped to 2p21-2p22. The CAPN13 mRNA exhibits a restricted tissue distribution with low levels of expression detected only in human testis and lung while CAPN14 mRNA could not be detected in any of the 76 tissues examined. Examination of the human genome sequence in the public and private consortia databases did not detect any further members of this gene family. Thus, there would seem to be 13 large subunit calpain genes in the human genome. Phylogenetic analysis reveals that the putative calpain large subunit proteins can be divided into three major groups. The 13 human large subunit genes and the single small subunit gene are located in eight syntenic groups on chromosomes 1, 2, 3, 6, 11, 15, 19 and X.

PMID: 11675017 [PubMed - indexed for MEDLINE]

1: Genomics 1998 Feb 15;48(1):117-20 Related Articles, Links

ELSEVIER SCIENCE FULL-TEXT ARTICLE

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**Matena K, Boehm T, Dear N.**

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CAPN5 and CAPN6 are recently identified human and mouse genes lacking a calmodulin-like domain with homology to the calpain family of proteases. To clarify their relationship to the known calpains, we have compared their genomi organization and chromosome location with other human calpain gene family members. In the mouse, both genes have 11 introns of identical location, with 6 of these being similar in location to those of the known vertebrate members. Surprisingly, there were no splice junctions in common with the nematode gene tra-3, the calpain with highest homology to CAPN5 and CAPN6. CAPN5 is localized on human chromosome 11, closely linked to the mu-calpain gene CAPN1. CAPN6, which is expressed only in the placenta, is localized on the X chromosome, to which no other calpain has yet been mapped.

PMID: 9503024 [PubMed - indexed for MEDLINE]

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US-PAT-NO: 6235481
DOCUMENT-IDENTIFIER: US 6235481 B1

TITLE: Polynucleotides encoding calpain 10

DATE-ISSUED: May 22, 2001

INVENTOR-INFORMATION:

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| Cox; Nancy J. | Inverness | IL | | |

US-CL-CURRENT: 435/6; 536/23.1, 536/24.1

CLAIMS:

What is claimed is:

1. An isolated and purified polynucleotide comprising a region encoding human calpain 10a, human calpain 10b, human calpain 10c, human calpain 10d, human calpain 10e, human calpain 10f, human calpain 10g, human calpain 10h, or mouse calpain 10.

2. The polynucleotide of claim 1, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, or SEQ ID NO:18.

3. The polynucleotide of claim 2, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:2.

4. The polynucleotide of claim 2, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:4.

5. The polynucleotide of claim 2, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:6.

6. The polynucleotide of claim 2, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:8.

7. The polynucleotide of claim 2, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:10.

8. The polynucleotide of claim 2, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:12.

9. The polynucleotide of claim 2, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:14.

10. The polynucleotide of claim 2, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:16.

11. The polynucleotide of claim 2, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:18.

12. The polynucleotide of claim 2, wherein the region has the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, or SEQ ID NO:19.

13. The polynucleotide of claim 12, wherein the region has the sequence of SEQ ID NO:1.

14. The polynucleotide of claim 12, wherein the region has the sequence of SEQ ID NO:3.

15. The polynucleotide of claim 12, wherein the region has the sequence of SEQ ID NO:5.

16. The polynucleotide of claim 12, wherein the region has the sequence of SEQ ID NO:7.

17. The polynucleotide of claim 12, wherein the region has the sequence of SEQ ID NO:9.

18. The polynucleotide of claim 12, wherein the region has the sequence of SEQ ID NO:11.

19. The polynucleotide of claim 12, wherein the region has the sequence of SEQ ID NO:13.

20. The polynucleotide of claim 12, wherein the region has the sequence of SEQ ID NO:15.

21. The polynucleotide of claim 12, wherein the region has the sequence of SEQ ID NO:17.

22. The polynucleotide of claim 12, wherein the region has the sequence of SEQ ID NO:19.

23. A vector comprising a polynucleotide that encodes human calpain 10a, human calpain 10b, human calpain 10c, human calpain 10d, human calpain 10e, human calpain 10f, human calpain 10g, human calpain 10h, or mouse calpain 10.

24. The vector of claim 23, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, or SEQ ID NO:18.

25. The vector of claim 24, wherein the region has the sequence of SEQ ED NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, or SEQ ID NO:19.

26. The vector of claim 25, wherein the region has the sequence of SEQ ID NO:1.

27. The vector of claim 25, wherein the region has the sequence of SEQ ID NO:3.

28. The vector of claim 25, wherein the region has the sequence of SEQ ID NO:5.

29. The vector of claim 25, wherein the region has the sequence of SEQ ID NO:7.

30. The vector of claim 25, wherein the region has the sequence of SEQ ID NO:9.

31. The vector of claim 25, wherein the region has the sequence of SEQ ID NO:11.

32. The vector of claim 25, wherein the region has the sequence of SEQ ID NO:13.

33. The vector of claim 25, wherein the region has the sequence of SEQ ID NO:15.

34. The vector of claim 25, wherein the region has the sequence of SEQ ID NO:17.

35. The vector of claim 25, wherein the region has the sequence of SEQ ID NO:19.

36. The vector of claim 23, further comprising a promoter.

37. The vector of claim 23, wherein the vector is a viral vector.

38. The vector of claim 23, wherein the vector is a retroviral vector.

39. The vector of claim 23, wherein the vector is a plasmid.

40. A recombinant host cell comprising a polynucleotide that encodes human calpain 10a, human calpain 10b, human calpain 10c, human calpain 10d, human calpain 10e, human calpain 10f, human calpain 10g, human calpain 10h, or mouse calpain 10.

41. The recombinant host cell of claim 40, further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, or SEQ ID NO:18.

42. The recombinant host cell of claim 41, wherein the region has the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, or SEQ ID NO:19.

43. The recombinant host cell of claim 42, wherein the region has the sequence of SEQ ID NO:1.

44. The recombinant host cell of claim 42, wherein the region has the sequence of SEQ ID NO:3.

45. The recombinant host cell of claim 42, wherein the region has the sequence of SEQ ID NO:5.

46. The recombinant host cell of claim 42, wherein the region has the sequence of SEQ ID NO:7.

47. The recombinant host cell of claim 42, wherein the region has the sequence of SEQ ID NO:9.

48. The recombinant host cell of claim 42, wherein the region has the sequence of SEQ ID NO:11.

49. The recombinant host cell of claim 42, wherein the region has the sequence of SEQ ID NO:13.

50. The recombinant host cell of claim 42, wherein the region has the sequence of SEQ ID NO:15.

51. The recombinant host cell of claim 42, wherein the region has the sequence of SEQ ID NO:17.

52. The recombinant host cell of claim 42, wherein the region has the sequence of SEQ ID NO:19.

53. The recombinant host cell of claim 40 wherein the host cell is further defined as a prokaryotic cell.

54. The recombinant host cell of claim 40, wherein the host cell is a eukaryotic cell.

55. The recombinant host cell of claim 54, wherein the host cell is a mammalian cell.

56. The recombinant host cell of claim 55, wherein the host cell is a human cell.

57. A method of obtaining a human calpain 10a, human calpain 10b, human calpain 10c, human calpain 10d, human calpain 10e, human calpain 10f, human calpain 10g, human calpain 10h, or mouse calpain 10 polypeptide comprising:

a) obtaining a polynucleotide comprising a region encoding a human calpain 10a, human calpain 10b, human calpain 10c, human calpain 10d, human calpain 10e, human calpain 10f, human calpain 10g, human calpain 10h, or mouse calpain 10;

b) inserting the polynucleotide into a host cell; and

c) culturing the host cell under conditions sufficient to allow production of the human calpain 10a, human calpain 10b, human calpain 10c, human calpain 10d, human calpain 10e, human calpain 10f, human calpain 10g, human calpain 10h, or mouse calpain 10 polypeptide;

wherein a human calpain 10a, human calpain 10b, human calpain 10c, human calpain 10d, human calpain 10e, human calpain 10f, human calpain 10g, human calpain 10h, or mouse calpain 10 polypeptide is thereby obtained.

58. The method of claim 57, further comprising the step of isolating the human calpain 10a, human calpain 10b, human calpain 10c, human calpain 10d, human calpain 10e, human calpain 10f, human calpain 10g, human calpain 10h, or mouse calpain 10 polypeptide from the host cell.

59. The method of claim 57, wherein the polynucleotide is further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, SEQ ID NO:12, SEQ ID NO:14, SEQ ID NO:16, or SEQ ID NO:18.

60. The method of claim 57, wherein the polynucleotide is further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:2.

61. The method of claim 57, wherein the polynucleotide is further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:4.

62. The method of claim 57, wherein the polynucleotide is further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:6.

63. The method of claim 57, wherein the polynucleotide is further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:8.

64. The method of claim 57, wherein the polynucleotide is further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:10.

65. The method of claim 57, wherein the polynucleotide is further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:12.

66. The method of claim 57, wherein the polynucleotide is further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:14.

67. The method of claim 57, wherein the polynucleotide is further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:16.

68. The method of claim 57, wherein the polynucleotide is further defined as comprising a region encoding an amino acid sequence as set forth in SEQ ID NO:18.

69. The method of claim 57, wherein the region has the sequence of SEQ ID NO:1, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:7, SEQ ID NO:9, SEQ ID NO:11, SEQ ID NO:13, SEQ ID NO:15, SEQ ID NO:17, or SEQ ID NO:19.

70. The method of claim 69, wherein the region has the sequence of SEQ ID NO:1.

71. The method of claim 69, wherein the region has the sequence of SEQ ID NO:3.

72. The method of claim 69, wherein the region has the sequence of SEQ ID NO:5.

73. The method of claim 69, wherein the region has the sequence of SEQ ID NO:7.

74. The method of claim 69, wherein the region has the sequence of SEQ ID NO:9.

75. The method of claim 69, wherein the region has the sequence of SEQ ID NO:11.

76. The method of claim 69, wherein the region has the sequence of SEQ ID NO:13.

77. The method of claim 69, wherein the region has the sequence of SEQ ID NO:15.

78. The method of claim 69, wherein the region has the sequence of SEQ ID NO:17.

79. The method of claim 69, wherein the region has the sequence of SEQ ID NO:19.

80. The method of claim 57, wherein the polynucleotide is comprised in a vector.

81. The method of claim 80, wherein the vector comprises a promoter.

82. The method of claim 80, wherein the vector is a viral vector.

83. The method of claim 80, wherein the vector is a retroviral vector.

84. The method of claim 80, wherein the vector is a plasmid.

85. The method of claim 57, wherein the host cell is further defined as a prokaryotic cell.

86. The method of claim 57, wherein the host cell is a eukaryotic cell.

87. The method of claim 86, wherein the host cell is a mammalian cell.

88. The method of claim 87, wherein the host cell is a human cell.